Brief Communication

Coexistence of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome in 46, XX female: A case report and review of literature

Viral N. Shah, Parth J. Ganatra[1], Rajni Parikh[2], Panna Kamdar[3], Seema Baxi[4], Nishit Shah[5]

Barbara Davis Center for Diabetes, Aurora, Colorado, [1]Primary Care Physician, Bhavnagar, [2]Department of Gynecology, [3]Medicine, and [4]Pathology, Government Medical College and Sir T Hospital, Bhavnagar, Gujarat, India, [5]Resident, Phoenix Children's Hospital, University of Phoenix, USA

ABSTRACT

The association of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome is very rare. We report a 21-year-old phenotypical female who presented with primary amenorrhea and underdeveloped secondary sexual characteristics. Hormonal evaluation revealed hypergonadotropic hypogonadism. Her karyotype was 46XX. Laparoscopy of pelvis revealed absent uterus, normal fallopian tubes and bilateral streak ovaries, which were biopsied and histopathology was consistent with the findings of gonadal dysgenesis. We searched PubMed for similar reports in the literature and details of all the cases were analyzed and reported here.

Key words: Gonadal dysgenesis, Mayer-Rokitansky-Kuster-Hauser syndrome, hypogonadism, primary amenorrhea

Introduction

Gonadal dysgenesis in female is defined as absent or insufficient development of ovaries.[1] The patient with gonadal dysgenesis presents with primary amenorrhea and lack of development of secondary sexual characteristics due to inability of ovaries to produce sex steroids. The karyotype in patients with gonadal dysgenesis can be 46XX, 45XO, mosaicism or deletion of a certain part of X chromosome.[1]

Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS) is characterized by absent or hypoplastic uterus and upper two third of the vagina in phenotypically and karyotypically normal female with incidence of approximately 1 in 5,000 newborn girls.[2] The female with MRKHS has normal secondary sexual characteristics due to normally functioning ovaries. It is the second most common cause of primary amenorrhea.

The coexistence of gonadal dysgenesis and MRKHS, though has been reported, remains rare.[1-23] Though the association between two entities is considered as coincidental, we have hypothesized few theories based on literature studies detailed here. We report here a case and reviewed all available literature to highlight presentations, karyotype abnormalities and gonadal abnormalities in these patients.

Case Report

A 21-year-old female was evaluated in our clinic because of primary amenorrhea and poor breast development. She is a child of non-consanguineous parents. Her birth event, perinatal and neonatal period were uneventful. Her growth and development were normal with normal intelligence. At the time of presentation, her height was 160 cm and weight 47 kg. On examination, there was no facial dysmorphism, no features suggestive of Turner syndrome like webbing of the neck or wide carrying angle. No skeletal deformity was found. Her blood pressure was

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Corresponding Author: Dr. Viral N. Shah, 33, New People Society, Subhash Nagar, Ring Road, Bhavnagar - 364 001, Gujarat, India.
E-mail: viralshah_rational@yahoo.co.in

110/70 mmHg in both arms. Her pubic hair and breast development were in tanner 3 stage and there was scanty axillary hair. Genital examination revealed blind vaginal pouch. She had history of seizure at the age of 19 years and she is on antiepileptic medications. Her hemoglobin was 11.2 g/dl with normal differentials. Her renal function tests and liver function tests were normal. Hormonal evaluation showed elevated follicle-stimulating hormone (100 IU/L) and luteinizing hormone (32 IU/L) with undetectable estradiol (<5 pg/ml) and testosterone (<0.1 ng/ml). Her serum thyroid stimulating hormone (2.3 mIU/ml) and cortisone (10 μg/dl) levels were normal. Ultrasound of pelvis did not show uterus or ovaries. Laparoscopy revealed absent of uterus, normal fallopian tubes and streak ovaries. Her computed tomography scan of the brain revealed bilateral periventricular and corona radiata hypointensity with undulation of both lateral ventricles suggestive of ischemic insult, rest of brain parenchyma and pituitary were normal. Her karyotype, obtained from peripheral blood lymphocytes by G-staining, was 46XX (20 cell lines). We obtained ovarian samples during laparoscopy and histopathology of ovarian tissues revealed streak ovaries. We confirmed coexistence of two disorder namely, gonadal dysgenesis and MRKHS in this patient. She was put on ethinyl estradiol 10 μg/day, daily for development of secondary sexual characteristics and bone health.

Discussion and Literature Review

Gonadal dysgenesis is the most common cause of primary amenorrhea and absent secondary sexual characteristics.[1] Gonadal dysgenesis may arise from early defect in primordial follicle formation or defect in differentiation of the ovary. The molecular basis of this condition is still not known. Patient with gonadal dysgenesis may have chromosomal abnormalities ranging from aneuploidy to microdeletion in X-chromosome.

MRKH is heterogeneous disorder characterized by uterovaginal atresia in 46XX female. Abnormalities of the genital tract may range from upper vaginal atresia to complete mullerian agenesis and may be associated urinary tract and/or skeletal abnormalities. Although, initially hypothesized to be due to abnormal activation of anti-mullerian hormone (AMH) expression or AMH receptor signaling in the female fetus, but no mutation in either AMH or AMH R have been found.[24] Mutations in WNT4 clearly involved in mullerian duct genesis, but it is not the main factor responsible for MRKH.[25]

Association between gonadal dysgenesis and MRKH has been reported in the literature, but very rare. Our extensive literature search showed 23 published cases presented with these two abnormalities. We reviewed all the cases in detail and are summarized in Table 1.

Our extensive literature search revealed 23 such published reports till date.[1-23] One case report was published in French language and hence was not possible for us to analyze it[5] and one case report could not be retrieved, so it was not included in the review.[22] Hence, total of 21 published case reports involving 26 patients were analyzed here for presentation, phenotypical and karyotypic abnormalities.

In all 23 cases, except one,[17] patients were presented in adult age with the complaint of primary amenorrhea and underdeveloped secondary sexual characteristics. In five case reports, there was history of consanguinity.[2,3,7,12,20] In 11 case reports, ovaries were absent[2,4,9,11,13,15-17,20,21,23] while in nine case reports ovaries were present, but dysgenetic.[1,3,7,8,12,14,18-20] There were three case reports, in which ovary on one side was either absent or dysgenetic and on the other side, it was normal.[6,9,10] In 15 case reports, uterus was absent[1,3,4,6-8,10,13-16,18,19,21,23] while in others it was present, but hypoplastic.[2,3,9,11,12,17,20] Similarly, fallopian tubes were normal in four case reports[7,8,15,16] but most reported hypoplastic or rudimentary fallopian tubes.[1-3,9,10,12-14,18,20,23] Urological abnormalities were present in four case reports including single kidney or malrotation of kidney and double ureter.[6,10,13,23] Skeletal abnormalities such as kyphosis, scoliosis, short phalanx or vertebral deformities were present in six case reports.[2,4,9,11,12,14] Four case reports including eight patients had alopecia.[2,3,12,20] Three cases had turner like features.[4,11,21] Only five case reports had a positive family history for gonadal and or mullerian abnormalities.[2,3,12,18,20] In 15 case reports, patients had normal 46, XX karyotype[1-3,5-10,12,13,17,18,20,23] while others had microdeletion or mosaicism.[4,11,14,15,16,21] These details are given in Table 1.

Our case is similar to reported by few, but differs from others. Based upon review of these cases, we could not exactly correlate any of the clinical findings or any somatic abnormalities with chromosomal findings. However, we feel there may be three possibilities beside just coincidence of coexistence of gonadal dysgenesis and mullerian abnormalities; first, there may be mutation or deletion of common genes involved in development and migration of germ cells and mullerian derivatives. Second, microdeletion in part of X-chromosome may result into absent or dysfunctional protein, which may interrupt the development of gonads and mullerian structures; third, possibility of endocrine disruptors cannot be ruled out. Since, none of the case reports have focused history towards substance/chemicals, which may behave like

Table 1: Literature review of published cases of combined gonadal dysgenesis and MRKH syndrome

Author (year)	Age of presentation (years)	Ovaries	Uterus	Fallopian tubes	Other abnormality	Keryotype
Bousfiha *et al*. (2010)[1]	19	D	-	-	None	46XX
Tatar *et al*. (2009)[2]	2 sisters	A	Hypoplasia	Hypoplasia	Partial alopecia, mild mental retardation, microcephaly, flat occiput, sparse eyebrows, mild-moderate dorsal kyphosis, thin upper lip and unilateral sensorineuraldeafness in one of them	46XX
Zamanand Nisar (2009)[3]	2 sisters (22 and 23)	D	One absent, another, rudimentary	Hypoplastic	Hypoplastic vagina, alopecia totalis	46XX
Güven *et al*. (2008)[4]	17	A	-	NR	Short stature, bone age was 12, hypertrophy of both second toes, down slanting palpebral features, webbed neck, low posterior hairline, cubitusvalgus, short 4th metacarpal	45, X/46, X, del (X) (p11.21)
Kumar *et al*. (2007)[6]	18	Right side, A	-	NR	Solitary malrotated pelvic kidney with PUJ obstruction	46, XX
Colombani *et al*. (2007)[7]	15	D	-	N	Autoimmune thyroiditis with secondary hypothyroidism	46XX
Marrakchi *et al*. (2004)[8]]	19	D	-	N	None	46XX
Plevraki *et al*. (2004)[9]	6 patients	Pt. no 1: Left side, A Pt. no 6: A	Pt. no 1: Hypoplastic uterus with symmetrical uterine buds, with no endometrium Pt. no 6: Uterus, symmetrical hypoplastic	Pt. no 1: Left fallopian tube, absent Pt. no 6: Both fallopian tube were symmetric, but hypoplastic	Pt. no 1: Short fourth metacarpal Pt. no 6: Anterior displacement of the third cervical vertebra, bifid first sacral vertebra, and lumbar scoliosis	46XX with testis specific protein 1-Y linked gene (in Pt. 1 and 4)
Kaya *et al*. (2003)[10]	17	Left, A	-	Right, normal. Left, hypoplastic	Right kidney, below normal level with malrotation	46XX
Aydos *et al*. (2003)[11]	19	A	Rudimentary	NR	Short and webbed neck, mild torticollis, cutis marmotara, mild hallux valgus, first metacarpal mildly displaced laterally	46, X, del (X) (pter->q22)
Mégarbané *et al*. (2003)[12]	2 sisters	D	Hypoplastic	Hypoplastic	Microcephaly, flat occiput, partial alopecia	46XX
Gorgojo *et al*. (2002)[13]	17	A	-	-	Single pelvic kidney, primary subclinical hypothyroidism	46XX
Ting and Chang (2001)[14]	22	D	-	Rudimentary	Scoliosis of the thoracic spine	45x/46x, del (X) (p22.22)
Güitrón-Cantú *et al*. (1999)[15]	19	A	-	N	None	45, X/46, Xdic (X)
Abelardo *et al*. (1999)[16]	19	A	-	N	None	45, X/46, Xdic (X)
Oyer *et al*. (1994)[17]	Neonate	A	Defects in mullerian derivatives	NA	Diaphragmatic hernia, bicuspid aortic valve	46XX
Aughton (1993)[18]	NA	D	-	-	The girl, mother, and maternal grandmother each have low galactose-1-phosphate uridyltransferase activities and are each heterozygous for the “classic” galactosemia allele	46XX
Alper *et al*. (1985)[19]	16	D	-	NA	Normal vagina	NA
Al-awadi *et al*. (1985)[20]	2 sisters (18 and 16)	One, A. Another, D	Hypoplastic	One, absent. Another, hypoplastic	Partial alopecia consisting of cranial hair only in the centre of the scalp	46XX
De Leon *et al*. (1984)[21]	NA	A	-	NR	Short stature, subtle features of turner syndrome	46, X, i (Xq)
Levinson *et al*. (1976)[23]	17	A	-	Absent	Absent vagina, double ureter on the left	46XX

PUJ: Pelvi-ureteric junction, NR: Not reported, A: Agenesis, D: Dysgenetic, +: Present, -: Absent, N: Normal, NA: Information not available or not retrievable

endocrine disruptors; it is difficult to ascertain their role in this abnormality.

In conclusion, coexistence of gonadal dysgenesis and MRKHS in a patient is rare. There is no correlation between chromosomes and phenotypical abnormalities. Some part of the X-chromosome or transcription factor or protein might have a role in regulating the skeletal, genital, urinary and gonadal development and deletion or mutation of that regulatory gene or its product may be responsible for coexistence of gonadal dysgenesis and MRKHS in an individual.

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